REMARKS

Claims 15-35 are currently pending in the present application. Table 1 on page 5 of the instant specification has been amended to indicate the sequences of the antisense oligonucleotides as disclosed in the application. Support for these amendments can be found in the specification, for example at page 4, lines 4-7 and lines 29-30; page 16, lines 2-7; page 23, lines 13-15; and Figure 7. The specification has additionally been amended to insert the appropriate SEQ ID NO. identifiers with the respective sequence listings. Further, a new sequence listing is submitted herewith as required under 37 CFR 1.821(g). Additionally, Applicants submit herewith substitute specification pages with the corrections already made for the Examiner's convenience.

The claims have additionally been amended in the expectation that the amendments will place this application in condition for allowance. The amendments do not introduce new matter within the meaning of 35 U.S.C. §132. Accordingly, entry of the amendments is respectfully requested.

The presently pending claims relate to compositions containing an antisense deoxyoligonucleotide having a sequence according SEQ ID NO: 1 (Oligo 83) or SEQ ID NO: 2 (Oligo 86) and a pharmaceutically acceptable carrier or diluent in combination with

an antiproliferative drug, an anticancer agent or a thymidylate synthase (TS) inhibitor. The claims also relate to methods of using the compositions and the combinations to treat cancer, to inhibit tumor cell growth or proliferation, to sensitize mammalian tumor cells to anticancer agents or to inhibit TS expression in mammalian cells.

1. Rejection of Claims 15-35 under 35 U.S.C. §112, 2nd paragraph

The Official Action states that claims 15-35 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter which Applicant regards as the invention. Applicants respectfully traverse this rejection. In particular, the Examiner asserts at page 3, lines 2-5 of the Official Action that, "contrary to the Applicant's assertions, the sequences according to SEQ ID NO: 1-2 represent target regions of TS mRNA, and do not represent sequences that would hybridize 'antisense' or a reverse compliment of the targeted regions of TS mRNA."

Applicants respectfully traverse this rejection. Regarding the §112, second paragraph rejection, case law has defined two requirements under the statute: (1) whether the Applicant has stated the invention as something elsewhere in the application which would not fall under the scope of the claims; and (2) whether

the claims would be communicated with a reasonable degree of particularity and distinctness to a person skilled in the art in light of the content of the disclosure and the teachings of the prior art. MPEP §2171, §2173, and §2173.02.

Contrary to the Examiner's assertions, Applicants respectfully submit that one skilled in the art would understand that the targeted mRNA of the presently claimed invention is sense to the cDNA indicated in Figure 7. Moreover, the skilled technician would understand that the presently pending claims pertain to pharmaceutical compositions containing, combinations of, and methods of using oligonucleotides complementary (i.e., antisense) to the delineated regions of the mRNA as represented by the cDNA in Figure 7.

In particular, the instant specification states at page 4, lines 4-7 that, "An antisense oligonucleotide is an oligonucleotide which is designed to hybridize to a specific region of a targeted nucleic acid sequence. The targeted nucleic acid is the TS gene or mRNA transcribed from the TS gene. Preferably the targeted nucleic acid is the mRNA encoding thymidylate synthase."

Further, throughout the instant specification are presented numerous provisions of support for Applicants' assertion that the presently claimed invention comprises antisense oligonucleotides

complementary to the TS cDNA/mRNA of Figure 7. For example, the instant specification references the GenBank sequence accession no. X02308. As evidenced by a printout for this accession number, a courtesy copy of which is attached for the Examiner's convenience, this entry in GenBank is defined as "Human mRNA for thymidylate synthase". Further, the identical sequence as that provided in GenBank is sourced from Takeishi et al., as referenced in the instant specification at page 27, line 26, and disclosed in the application, in part in Figure 7. The Examiner is reminded that a reference in a patent specification to a deposit in a public repository (such as the GenBank sequence described above) is sufficient to constitute an adequate description of the deposited material to satisfy the requirements of 35 U.S.C. 112. See Enzo Biochem, Inc. v. Gen-Probe, Inc., 63 U.S.P.Q.2d 1609 (Fed. Cir. 2002).

Similarly, the instant specification describes the antisense oligonucleotides of the invention "using the sequence numbering described for human thymidylate synthase mRNA by Takeishi et al., 1985" (page 3, lines 24-25 and page 4, lines 1-3). For example, page 16, lines 2-4 states that Oligo 86 (SEQ ID NO: 2) is "complementary to TS mRNA from base pair positions 1035 to 1054 (GenBank accession no. X02308; Takeishi *et al.*, 1985), which

surround the TS mRNA translation stop site (UAG at bases 1045 to 1047)." Accordingly, the repeated references in the instant specification to the antisense oligonucleotides of the invention as "targeted" to or "complementary" to the sequence of GenBank sequence accession no. X02308 supports Applicants' assertion that the presently claimed compositions, combinations, and methods comprise antisense oligonucleotides complementary to the TS cDNA/mRNA of Figure 7.

Additionally, page 23, lines 10-14 of the instant specification describes the phosphorothiorated oligonucleotide of SEQ ID NO: 1 (termed ODN 83) as "complementary to TS mRNA, starting from a position 136 base downstream of the translation stop site (5'-GCCAGTGGCAACATCCTTAA-3')." Accordingly, the instant specification provides explicit support for the sequences of the antisense oligonucleotides comprised within the presently claimed compositions, combination products, and methods of use. Likewise, the instant specification also describes examples employing oligonucleotides antisense to regions of the TS mRNA in combination with an anticancer agent, Tomudex, for example, at page 21, lines 17-19.

Applicants have accordingly amended Table 1 on Page 5 of the instant specification and provided a replacement sequence listing

indicating the sequences of the antisense oligonucleotides disclosed in the application, as described above. Further support for these amendments can be found in the specification, for example at, lines 4-7 of page 16.

Applicants submit, then, that the presently claimed invention does in fact comprise compositions, combinations products, and methods of using antisense oligonucleotides complementary to the TS cDNA/mRNA of Figure 7, contrary to the Examiner's assertion. The instant specification provides numerous instances of support for this assertion.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of pending claims 15-35.

2. Rejection of Claims 15-35 under 35 U.S.C. §112, 1st paragraph

The Official Action states that claims 15-35 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In particular, the Examiner asserts that the "specification fails to provide sufficient guidance to the skilled artisan on the parameters for practicing a method of nucleic acid therapy in an

individual *in vivo* comprising administration of a complex comprising TS antisense oligonucleotides for the breath of the claimed invention." Further, the Examiner maintains that Applicants need to provide evidence that the presently claimed antisense pharmaceutical compositions and methods for treatment produce a therapeutic effect *in vivo* as well as guidance on how to produce this effect without undue experimentation.

Applicants respectfully traverse this rejection. In order to make an enablement rejection, the Examiner has the initial burden to establish a *reasonable* basis to question the enablement provided for the claimed invention. *In re Wright*, 27 USPQ2d 1510 (Fed. Cir. 1993). The test under 35 U.S.C. § 112, first paragraph, for determining compliance with the enablement requirement is whether one skilled in the art could make or use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation. *United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988).

Initially, Applicants traverse the Examiner's assertion that the antisense deoxyoligonucleotides sequences recited in the presently claimed compositions, combination products, and methods of use are not antisense sequences. Instead, as Applicants have shown in section 1 above, the arguments of which are herein

incorporated by reference in their entirety, these sequences are in fact antisense sequences.

Further, in reply to the Examiner's requirement for *in vivo* evidence, Applicants remind the Examiner that, as stated in the Response to Official Action of March 5, 2002, "*in vivo* data is not required under 35 U.S.C. §112, first or second paragraph. A specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as if in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971); MPEP 2107.01."

However, for the Examiner's information, Applicants further enclose with this response a courtesy copy for the Examiner's review of the following journal article disclosing an *in vivo* study showing that systemic treatment with TS antisense ODN 83 significantly inhibited (HT29 human colon carcinoma cell) tumor growth in mice published by the present Applicants. The reference is as follows, Berg, R.W., et al., "Tumor Growth Inhibition *in Vivo*

an G2/M Cell Cycle Arrest Induced by Antisense Oligodeoxynucleotide Targeting Thymidylate Synthase", (2001) *J. of Pharmacology and Experimental Therapeutics*, 298 (2), 477-484.

The Examiner's attention is respectfully directed to the experimental protocol ("Animal Studies") portion of this journal article, which indicates that tumors were first established by subcutaneous injection of cancer cells in mice and Oligo 83 subsequently injected intraperitoneally into the mice. The results of the animal studies indicate that Oligo 83 was able to retard tumor growth.

Accordingly, in view of Applicants own additional published *in vivo* data demonstrating the ability of the presently claimed antisense deoxyoligonucleotides to effectively retard tumor growth, Applicants assert that one skilled in the art would have a reasonable expectation, based on the teachings in the application, that the invention would work as claimed without the application of undue experimentation. The Examiner is reminded that a specification must be viewed as enabling unless the Examiner is able to provide evidence to the contrary (*In re Wright*). In view of this additional *in vivo* data, the Examiner has no basis for asserting that the present specification is non-enabling unless she can provide specific evidence to the contrary.

Accordingly, Applicants respectfully request the Examiner to reconsider and withdraw the rejection of pending claims 15-35.

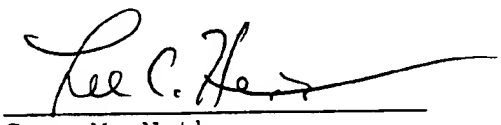
CONCLUSION

Based upon the foregoing amendments and remarks, the presently claimed subject matter is believed to be enabled, novel, and patentably distinguishable over the prior art of record. The Examiner is therefore respectfully requested to reconsider and withdraw the outstanding rejections and allow all pending claims 15-35 presented herein for reconsideration. Favorable action with an early allowance of the pending claims is earnestly solicited.

The Examiner is invited to telephone the undersigned attorney if she has any questions or comments.

Respectfully submitted,

NATH & ASSOCIATES PLLC

Dated: September 16, 2003 By: 

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